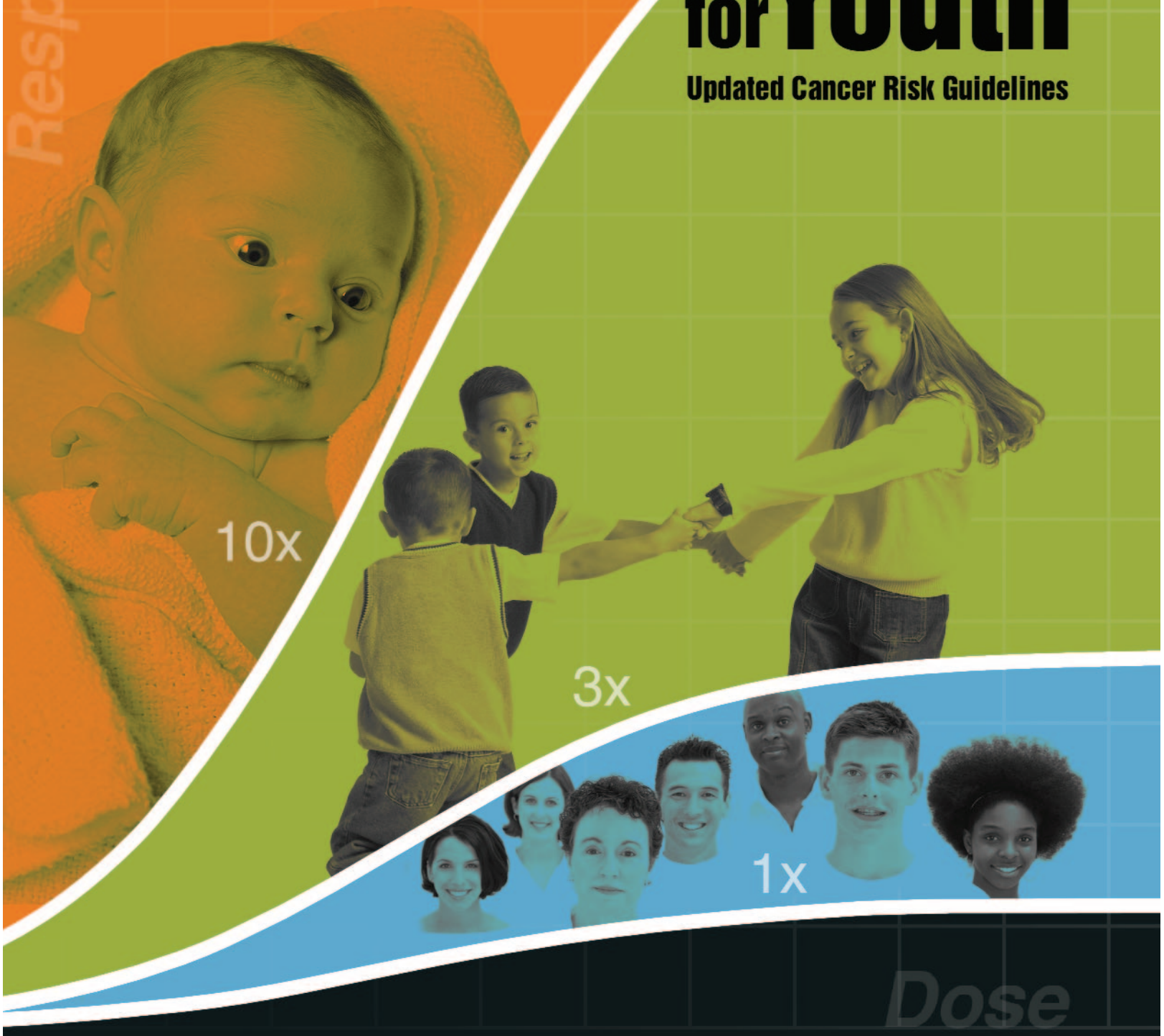
Adjusting for Youth

Updated Cancer Risk Guidelines



For several decades, scientists have gathered evidence suggesting that young children are more sensitive to the cancer-causing effects of some chemicals than adults. Now the U.S. Environmental Protection Agency (EPA) has taken the unprecedented step of incorporating that information into the methods it uses to assess risks posed by carcinogens. The agency is urging scientists to assume, when chemical-specific data are missing, that children under age 2 are 10 times more vulnerable to mutagenic carcinogens than adults, and that children aged 2–15 are 3 times more vulnerable. These additional "adjustment factors," when applied in risk assessments, could tighten regulatory standards for some chemical products, thereby reducing the potential for childhood exposures.

The new recommended approaches are contained in the EPA's draft *Supplemental Guidance for Assessing Cancer Susceptibility from Early-Life Exposure to Carcinogens*. "The supplement," as it is routinely called, accompanies the agency's most recent draft guidelines for cancer risk assessment, which are expected to be finalized early in 2004. Scientists from across the agency use these guidelines, which were last revised in 1999, as a handbook for current EPA methods on assessing cancer risks from environmental chemicals.

The draft supplement—a first of its kind at the EPA—was developed in response to a recommendation from the National Research Council and the EPA Science Advisory Board (SAB). "The supplement represents a significant departure from existing EPA approaches because it calls for an explicit assessment of children's risk," says William Wood, executive director of the EPA Risk Assessment Forum.

Wood says the supplement offers quantitative approaches based on a review of the currently available data that compare early life stage responses—including fetal responses—to those of adults. For its review, the EPA analyzed 23 peer-reviewed studies, extending back 50 years, of cancer incidence following exposure to mutagens, nonmutagens, and radionuclides.

The risk from childhood exposures to environmental chemicals is thought to be heightened for two reasons. First, children's behaviors make them prone to high exposures: they crawl on the ground, they put their fingers in their mouths, and they inhale more air per unit body weight than adults. Second, children's developing organ systems can be uniquely vulnerable to chemically induced changes.

The supplement addresses the latter situation. Limited animal data suggest that mutagenic carcinogens—which cause cancer by damaging DNA—can be particularly dangerous to children. Cells divide more frequently during development, which provides less time for DNA to repair itself after chemical attack. Some embryonic cells, such as brain cells, lack DNA-repair enzymes altogether.

A Focus on Mutagenic Chemicals

According to Wood, the supplement directs EPA scientists to use the new adjustment factors only when assessing mutagenic carcinogens. In other words, the factors are applied when a carcinogenic mode of action is known to be mutagenic and when there are no chemical-specific studies in young animals. Applying the factors represents a conservative approach that magnifies a carcinogen's calculated potency among the targeted age groups. According to Wood, use of these adjustment factors is justified by evidence showing that some mutagens (for instance, vinyl chloride and radionuclides that interact with DNA) pose more of a cancer threat during early life stages than during adulthood.

But even as the guidelines explicitly assume heightened cancer risk from childhood exposures, they also acknowledge that—for some carcinogens—the risks from childhood and adult exposures may be similar. Furthermore, the guidelines emphasize that nonmutagenic carcinogens may exhibit dose "thresholds" below which cancer risks among all humans are insignificant. This represents a continuation of the agency's efforts, first expressed in draft revisions to the 1996 version of the guidelines, to move away from the assumption of linearity to a more method-specific framework for dose–response assessment.

Says Wood, "The main thrust of the guidelines is that you should work your way through the data first. Based on that review, you should then determine if you have enough information to understand how a chemical induces cancer and the resulting likelihood for early life stage sensitivity." Such an understanding, he says, would aid scientists in evaluating the need to fall back on default assumptions.

According to the guidelines, if data show convincing evidence of a nonmutagenic mode of action in young animals, then alternative approaches that depart from assumptions of dose linearity—that is, that risk is proportional to dose—are warranted. These alternative methods implicitly assume the existence of a safe, low-dose exposure level below which risk of cancer is unlikely.

According to the draft guidelines, once carcinogenic potency (or dose response) has been evaluated, a chemical should be classified according to the following proposed hazard descriptors: "carcinogenic to humans," "likely to be carcinogenic to humans," "suggestive evidence of carcinogenic potential," "inadequate information to assess carcinogenic potential," and "not likely to be carcinogenic to humans."

A Question of Thresholds

Wood agrees that, as the guidelines indicate, the evidence on thresholds justifies nonlinear methods to assess risks from nonmutagenic carcinogens for both children and adults when sufficient mode-of-action data are available. However, stakeholder opinions on this point are far from unanimous.

Environmental groups suggest that toxicologists may not know enough about the range of mechanistic possibilities to set standards based on nonlinear assumptions. "How do you know when you have sufficient evidence to say a carcinogen has a threshold?" asks Jennifer Sass, a senior scientist with the Natural Resources Defense Council. "Scientists may focus disproportionately on one mode of action and ignore others that may be relevant to humans."

The guidelines recognize this problem, and stipulate that multiple modes of action should be considered to avoid this possibility, Sass says. But she is concerned that the guidelines don't provide enough guidance on how multiple modes of action should be evaluated.

Wood counters that EPA scientists don't yet know enough about nonmutagens to develop generic guidance on how to address them. A case-by-case approach to these chemicals is more suitable, he says. "Stakeholders always want guidelines to be more specific," Wood says. "But these documents [are designed to stay] in place for about a decade. By being overly specific and not anticipating the evolution of the science, you run the risk that the guidelines will quickly go out of date."

SAB Review

Currently, the supplement is being reviewed by the EPA SAB, a multistakeholder group of experts that provides input on agency activities. This review is still ongoing, and neither SAB members nor EPA staff will discuss how the comments are being addressed until deliberations are finished and a final version is made available to the public (this is expected by spring 2004). On 5 August 2003, the latest draft of the SAB comments were published on the EPA website. Based on that draft, it appears that the SAB agreed that human fetuses and children are uniquely sensitive to carcinogens and applauded the EPA's efforts to consider children as a distinct subset of the population.

However, contrary to the approach outlined in the supplement, the SAB recommends that the EPA extend the application of default adjustment factors to include nonmutagenic carcinogens when modes of action are unknown. George Lucier, former director of the NIEHS Environmental Toxicology Program, who cochaired a stakeholder group involved in the early stages of drafting the guidelines, says there is evidence to suggest that children can be more sensitive to nonmutagenic carcinogens than adults.

He cites the example of transplacental exposure to diethylstilbestrol, a synthetic hormone, which was shown to induce vaginal adenocarcinomas in girls during their teenage years by nonmutagenic hormonal disruption pathways. Adult women exhibit much less sensitivity to this chemical, he adds. Moreover, adult cancers do not include the vaginal variety observed in children. "The key point to make," he says, "is that children can be at higher risk even for threshold carcinogens"—that is, those that exert cancer-causing effects only when doses exceed an experimentally defined minimum.

Some additional SAB criticisms were noted, among them a suggestion that EPA scientists strengthen the evidence for early life stage sensitivity with a broader search of the literature. Furthermore, the SAB recommended that EPA scientists add a third age grouping (9–15 years) that would recognize puberty's potentially important vulnerabilities, such as increased hormonal activity.

The EPA is also considering public comments provided by numerous stakeholder interests. Among them are companies that could lose economically if the guidelines were to pass in their present form. Lucier says the use of child-specific adjustment factors could impact markets for some chemical products, for example by changing the amount of certain classes of pesticides that can be used in agriculture. Adjustment factors could also influence cleanup requirements for carcinogens at hazardous waste sites, thereby driving up the costs of remediation.

One group that represents agrochemical companies, in addition to other biotechnology interests, is CropLife America, a trade association based in Washington, D.C. Angelina Duggan, director of science policy at CropLife America, says industry welcomes the EPA's ongoing effort to move away from default assumptions. Her specific recommendation is that the EPA expand its hazard descriptors to include a category for chemicals that are "not carcinogenic to humans." Says Duggan, "If the mode of action tells you that's the case, then you should clearly state that."

Lucier says the new guidelines will put the onus on industry to demonstrate that fetuses and children are not, in fact, more sensitive to chemical products than adults. Most of the toxicology data generated today derive from two-year bioassays in adult rodents, he says. If companies want to avoid the new adjustment factors, he says, they will have to conduct full-lifetime exposure studies or convincing mechanistic studies that account for early life stage sensitivities.

According to Wood, the agency will continue to update its methods as new information becomes available. He emphasizes that the guidelines embody a "living document" designed to accommodate new scientific discoveries. "[Cancer risk assessment] is an evolving area," he says. "Millions of dollars are spent researching modes of action for individual chemicals, and I think we're much farther along in our mechanistic understandings. These guidelines provide us the ability to take that information into effect."

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